

**REMARKS**

On behalf of Applicants, the undersigned wishes to express appreciation to Examiner Sharareh for the telephonic interview granted on May 1, 2003. The opportunity for Applicants, the undersigned and Examiner Sharareh to discuss the various issues in this case was extremely helpful and it is believed that it will expedite the prosecution of this case.

The Examiner's Interview Summary is a fair reflection of what was discussed during the interview; however, the undersigned would like to add several comments to it. In addition to Applicants Alice C. Martino and Walter Morozowich, the third inventor in this case, Ernest J. Lee, also participated in the interview. In addition to the amendments referred to by the Examiner, the limiting of present Claim 1 and claims dependent therefrom to a tablet composition wherein the rapidly precipitating drug is a "fairly or highly soluble salt form of a poorly soluble free base or free acid" and adding claims wherein the rapidly precipitating drug is an "anhydrous form of a poorly soluble free base or free acid" was discussed. The significance of so restricting the present claims will be addressed in the discussion of the rejection of Claims 1-24, 26, 30 and 33-37 based upon the Makooi-Morehead et al patent (U.S. Patent No. 6 238 695). Finally it was agreed that by amending the claims to recite that the "rapidly precipitating drug" was the sole active pharmaceutical ingredient in the tablet composition would clarify that the claims excluded tablet compositions that contain more than one active pharmaceutical ingredient.

Claims 1-20, 22-24, 26, 30, 34-38 and 39-67 (newly added) are in the application.

Claims 35-37 stand rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claims 1-12, 21-24, 26, 30 and 33-38 stand rejected under 35 USC 102(b) as being anticipated by Elger et al, U.S. Patent No. 4 844 907.

Claims 1-24, 26, 30 and 33-37 stand rejected under 35 USC 102(e) as being anticipated by Makooi-Morehead et al, U.S. Patent No. 6 238 695.

Claims 1-24, 26, 30 and 33-38 stand rejected under 35 USC 103(a) as being unpatentable over Elger or Clorpress® Package Insert in view of Makooi-Morehead, U.S. Patent No. 6 238 695.

New Claims 39-67 have been added. New Claim 39 is replacing original Claim 1 as the generic claim. It is of the same breadth as original Claim 1, but it incorporates the amendments discussed during the telephonic interview of May 1, 2003.

Claim 1 has been made dependent upon new Claim 39 and is limited to a tablet composition wherein the rapidly precipitating drug is a "fairly soluble or highly soluble salt form of a poorly soluble free base or acid."

New Claim 40 and claims dependent therefrom are limited to a tablet composition wherein the rapidly precipitating drug is an "anhydrous form of a poorly soluble free base or free acid."

Support for the rapidly precipitating drug recited in Claims 1 and 40 find support on page 3, lines 16-19 of the specification, hence, and does not constitute new matter.

New Claims 40-67 also do not add new matter. They simply further define compositions wherein the rapidly precipitating drug is an anhydrous form of a poorly soluble free base or free acid and they mirror dependent Claims 2-24, 26, 30 and 33-38 that define compositions wherein the rapidly precipitating drug is a "fairly soluble salt or highly soluble salt of a poorly soluble free base or free acid."

THE REJECTION OF CLAIMS 35-37  
UNDER 35 USC 112, SECOND PARAGRAPH

Deleting "microcrystalline cellulose" has amended claim 35. Therefore, this rejection is no longer applicable.

THE REJECTION OF CLAIMS 1, 12, 21-24, 26, AND 34-38  
UNDER 35 USC 102(b) AS BEING ANTICIPATED BY  
ELGER ET AL, U.S. PATENT 4 844 907

Claims 1, 12, 21-24, 26, and 34-67 are not anticipated by Elger et al, U.S. Patent No. 4 844 907 ('Elger et al'). To constitute an anticipation of a claim, a single reference must disclose every limitation of the claim.

Present Claim 39 defines:

A non-sustained release, non-chewable tablet composition, which comprises a rapidly precipitating drug, and only a rapidly precipitating drug as the sole active pharmaceutical ingredient, in an amount from about 5 to 60%, a polymeric binder in an amount from about 2 to about 25%, a superdisintegrant in an amount from about 6 to about 40% and a lubricant in an amount up to about 5%; (a) wherein the rapidly precipitating drug is a fairly soluble or highly soluble salt form of a poorly soluble free base or free acid, or an anhydrous form of a poorly soluble free base or free acid, that is prone to supersaturation when introduced in water, or simulated physiological fluids at body temperature, begins to dissolve fairly rapidly and then begins to rapidly precipitate out of solution and (b) wherein more than 90% of the rapidly precipitating drug precipitates out within 60 minutes after coming into contact with said water or simulated physiological fluids at body temperature, with the proviso that the rapidly precipitating drug is not delavirdine mesylate.

As agreed during the telephone interview, Claim 39 recites a "polymeric binder", a superdisintegrant and a lubricant as positive limitations and recites that the rapidly precipitating drug is the sole active pharmaceutical ingredient in the tablet formulation. All of these added

limitations are disclosed in the specification and hence do not constitute new matter.

Elger et al is directed to a bilayered tablet that contains two active pharmaceutical ingredients (a narcotic analgesic and a non-steroidal anti-inflammatory compound). Since the Elger et al tablet composition does not contain a single active pharmaceutical ingredient, it does not anticipate the tablet composition of Claim 39. Claims 1-12, 21-24, 26, 30 and 34-67 are dependent from Claim 39 and contain all of its limitations, hence they are not anticipated by Elger et al for the same reasons that Claim 39 is not. The claims further require the presence of a lubricant in an amount of up to 5%. The self-lubricating compression aid in the Elger et al composition is always present in an amount above 10%. Claims 22-24 further require that the lubricant be selected from the group consisting of magnesium stearate and stearic acid. Elger et al states that their tablet is free of stearic acid or stearate salts (Column 1, lines 35-40 and lines 49-65). Claims 35-37, 64 and 66 require that the tablet be made without heating, solvent or grinding. Elger et al prepare their tablet composition utilizing wet granulation wherein water is used as a solvent.

In the paragraph bridging pages 3 and 4 of the Office Action, the Examiner states "that the pending claims are drafted in the form of product by process" and "the process steps are not limiting to the product instantly claimed so long as the product of the prior art is the same as those instantly claimed." This assertion is not correct for two reasons: (1) Claims 35-37 and new Claims 64 and 66 are the only product-by-process claims in the application. (2) As pointed out above in the discussion of Elger et al and as will be shown in the discussion of the other prior art cited against the claims, the prior art tablet compositions are not the same product as the claimed tablet composition.

THE REJECTION OF CLAIMS 1-24, 26 AND 34-67

AS BEING ANTICIPATED BY

MAKOOI-MOREHEAD ET AL, U.S. PATENT NO. 6 238 695

Makooi-Morehead et al does not anticipate Claim 39 because it does not contain all of the limitations of Claim 39.

Makooi-Morehead et al discloses a capsule or compressed tablet that may comprise the following components:

- (a) a therapeutically effective amount of efavirenz
- (b) a surfactant
- (c) a disintegrant
- (d) a binder
- (e) a diluent
- (f) a lubricant
- (g) a glidant
- (h) optionally additional pharmaceutically acceptable excipients

Present Claim 39 requires that the active pharmaceutical ingredient be a rapidly precipitating drug prone to forming a supersaturated solution when introduced in water, or simulated physiological fluids at body temperature. There is no teaching or suggestion by Makooi-Morehead et al that efavirenz is an anhydrous form of a hydratable drug and therefore capable of generating a supersaturated solution upon contact with water or physiological fluids at body temperature in the presence of HPMC or other polymeric binders.

The Examiner has asserted that microcrystalline cellulose is a binder; however, it is not a binder as that term is used in the instant application. An inventor is entitled to be his or her own lexicographer. A fair reading of the application makes it clear that microcrystalline cellulose is not included as one of Applicants' polymeric binders but is a separate ingredient. For example, note the following statements in the specification.

Page 2, lines 19-25:

"Disclosed is a non-sustained release pharmaceutical tablet composition which comprises: a rapidly precipitating drug in an amount from about 5 to about 60%, microcrystalline cellulose and at least one member selected from the group consisting of a binder in an amount of from about 2 to about 25% and a superdisintegrant in an amount from about 6 to about 40% where the rapidly precipitating drug, microcrystalline cellulose, binder and superdisintegrant are mixed and compressed into a tablet without heating, solvent or grinding."

Page 3, lines 5-9:

"The tablets of the present invention require a rapidly precipitating drug (5-60%), microcrystalline cellulose (10-50%), a binder (2-25%) and superdisintegrant (6-40%). While not required, it is often highly desirable to use one or more of the following pharmaceutical ingredients - microcrystalline cellulose (0-50%), lactose (0-80), a flow agent (0-5) and a lubricant (0-5%)."

Page 4, lines 10-11:

"It is preferred that the binder, microcrystalline cellulose and superdisintegrant all be present."

These statements in the specification, as well as original Claim 1, and the present claims make it clear that the applicants disclose microcrystalline cellulose and binder as two mutually exclusive components in the claimed invention.

While on page 4, line 3, microcrystalline cellulose is listed as a binder, it is obvious from reading the rest of the paragraph that it is not intended to be a binder since it is the only previously listed component that is not listed in the binders listed on page 4, lines 17-22.

Further evidence that microcrystalline cellulose is not one of the binders of the claimed tablet composition can be gleaned from page 4, lines 30-33 of the specification wherein it states:

"The microcrystalline cellulose is not absolutely necessary to prepare the tablet formulation of the present invention. However, it is highly desirable to have it present in most cases. The tablet formulation can use a microcrystalline cellulose diluent."

The polymeric binder and superdisintegrant are required components of the claimed tablet composition. The disclosure establishes that microcrystalline cellulose, when present, serves as a diluent in the claimed tablet composition.

Further evidence that microcrystalline cellulose is not a polymeric binder as that term is used in the instant application is provided by the Declaration of Dr. Martino, which is attached and made a part of this Response. Part of that Declaration is a plot that shows (1) the delay of precipitation profile of a soluble salt of a poorly soluble drug in the presence of a polymeric binder, HPMC (Curve A), (2) the precipitation profile of a soluble salt of a poorly soluble drug in the absence of HPMC (Curve B) and (3) the delay of precipitation profile of a soluble salt of a poorly soluble drug in the presence of microcrystalline cellulose and no HPMC (Curve C). The microcrystalline cellulose does not provide the delay of precipitation that is provided by HPMC (Curve A), a polymeric binder. This is described in Dr. Martino's Declaration, beginning on page 3, fifth full paragraph through page 4, fourth paragraph.

As explained by Dr. Martino during the telephonic interview, the binders described in the Makooi-Morehead patent are comprised of lactose, starch and various sugars (Column 3, lines 21-22). In the current common state of the art, these materials are more often considered to function primarily as diluents, since in their native forms their components merely provide a limited degree of tablet bond. In contrast, the term binder as used in our claims is the generally more effective polymeric binders as disclosed on page 4, lines 21 and 22 of the specification, wherein it is stated:

"It is apparent to those skilled in the art that the binders of the present invention are polymeric binders as opposed to non-polymeric binders."

Hence, the lactose, starch and various sugar binders disclosed in Makooi-Morehead et al are totally different from the polymeric binders defined in the claimed tablet composition. Further evidence that the binders disclosed by Makooi-Morehead et al is set forth in the Declaration of Dr. Alice C. Martino.

Claims 1-24, 26, 30, 34-67, all dependent from Claim 39, are not anticipated by Makooi-Morehead for the reason that Claim 39 is not. Claims 1-24, 26, 30 and 34-38 are further not anticipated by Makooi-Morehead et al because they all require that the rapidly precipitating drug be a "fairly soluble salt" or a "highly soluble salt" of a poorly soluble drug. The drug efavirenz is not a salt.

Claims 2-4, 34, 37, 41-44 and 65 are further not anticipated by Makooi-Morehead et al because they define specific polymeric binders, for example HPMC and PVP, that are not disclosed by Makooi-Morehead et al.

Claims 35-37, 64, 66 and 67 further are not anticipated by Makooi-Morehead et al because they require that the claimed tablet composition be manufactured without heating, solvent or grinding. In contrast, all disclosed examples (Examples 1-3) in Makooi-Morehead et al require the use of the solvent water as wet granulation.

REJECTION OF CLAIMS 1-24, 26, 30 AND 33-38  
UNDER 35 USC 103(a) AS BEING UNPATENTABLE OVER  
ELGER ET AL OR THE CLORPRESS® PACKAGE INSERT  
IN VIEW OF MAKOOI-MOREHEAD ET AL

These claims are patentably distinguishable over the combination of Elger et al or Clorpress® Package Insert in view of Makooi-Morehead et al for the following reasons. The Elger et al and Clorpress® references both describe tablets that require the presence of two active pharmaceutical ingredients, whereas the claimed tablet composition requires



the presence of a rapidly precipitating drug as the sole active pharmaceutical ingredient. The addition of the teaching of Makooi-Morehead et al does not and cannot cure this defect of the primary references. Further, the Clorpress® tablet does not contain a polymeric binder. As pointed out above in the discussion of the Makooi-Morehead et al patent, it does not disclose the use of polymeric binders, hence it does not cure this defect of the Clorpress® reference. Finally, one skilled in the art would not be led to combine the teaching of Makooi-Morehead et al with Elger et al because the Makooi-Morehead et al reference teaches the use of lubricants such as magnesium stearate in their tablet composition, whereas Elger et al teaches that such lubricants cannot be used in their tablet composition.

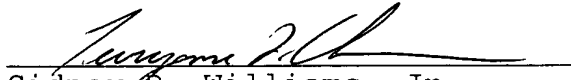
At the conclusion of this rejection, in the first paragraph of page 7 of the Office Action, the Examiner states:

"Nevertheless, it would have been obvious to one of ordinary skill in the art at the time of invention to employ lactose and colloidal silicone dioxide in suitable amounts within the compositions of Elger, or the formulation of Clorpress, and further optimize all concentrations in a tablet dosage form, because as taught by Makooi-Morehead, the ordinary artisan would have had a reasonable expectation of success in improving the rate of dissolution of a insoluble drug and subsequently its extent of absorption in GI track."

However, as explained by the inventors during the telephonic interview, improving the rate of dissolution of an insoluble drug is not the object of the claimed invention. The object of the claimed invention is to provide a non-sustained release, non-chewable tablet composition comprising (1) a rapidly precipitating drug that is prone to supersaturation in a form that is soluble in water or physiological fluids at body temperature and in combination with (2) a polymeric binder and disintegrant that will delay or slow down precipitation of the drug from water or a physiological fluid at body temperature.

In view of the above discussed amendments and arguments, withdrawal of the rejection and expeditious passage of this application is respectfully solicited.

Respectfully submitted,

  
for Sidney B. Williams, Jr.

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Encl: Declaration of Dr. Alice C. Martino  
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